5. (amended) The method of claim 1 wherein the molecule to be delivered is a nucleic acid molecule and the nucleic acid molecule is a gene or cDNA under the control of a promoter [which can be] expressed in the nucleus of an endothelial cell.

13. (amended) A conjugate of an agent binding selectively to endothelial protein C receptor (EPCR) selected from the group consisting of protein C, activated protein C, antibodies reactive with EPCR and fragments thereof binding to EPCR, and a molecule to be delivered to a large vessel endothelial cell, wherein the molecule is not a diagnostic label.

17. (amended) The conjugate of claim 16 wherein the nucleic acid molecule is a gene or cDNA under the control of a promoter [which can be] expressed in the nucleus of an endothelial cell.

19. (amended) The conjugate of claim 13 wherein the molecule to be delivered is [selected from the group consisting of drugs and diagnostic agents] a drug.

Remarks

Drawings

Formal drawings were mailed August 6, 1999.

Information Disclosure Statement

An Information Disclosure Statement is being submitted today under separate cover. Please note that copies of numerous publications have been submitted and are enclosed in a box due to the volume.

Rejections under 35 U.S.C. §112, first paragraph

Claims 1-10 and 12-25 have been rejected under 35 U.S.C. §112, as enabled for in vivo applications only. This rejection is traversed.

The basis of the argument is that even though the application demonstrates that conjugates of molecules binding to the endothelial protein C receptor (EPCR) can be made, delivered to cells, the conjugates bind to the EPCR, and the molecules be taken up by the EPCR and delivered into the nucleus, that one skilled in the art could not perform this method, *which is all that is required by the claims.*

The examiner has no authority to read limitations into, or broaden the claimed elements. The independent claims recite:

1. A method for selectively delivering molecules to the nucleus of endothelium of the large vessels, comprising

administering a conjugate of an agent binding selectively to endothelial protein C receptor (EPCR) and the molecule to be delivered to large vessel endothelial cells.

13. A conjugate of an agent binding selectively to endothelial protein C receptor (EPCR) and a molecule to be delivered to a large vessel endothelial cell.

The legal requirement under §112 is only that the claims be enabled to those skilled in the art – NOT that the claims be enabled for all possible purposes for which the claimed material might be used. Applicants have shown actual reduction to practice showing that the conjugates bind to the receptors, that the conjugates are taken up and the molecules delivered to the cell nucleus – no more is required.

The Examiner's "facts" recited on page 3 are in error.

1. "The quantity of experimentation necessary to reduce the instant claimed invention to practice would involve binding of a conjugate to an EPCR in vivo."

Based on what? Why? No evidence whatsoever has been provided in support of this conclusion.

2. "The nature of the invention is complex. The binding of molecules to EPC receptors has not been taught in the prior art, and use of ligands to deliver molecules to receptors on endothelial cells of large vessels is also not taught in the prior art."

The former is simply untrue; the latter is the claimed invention and is shown in the examples (which are endothelial cells of large vessels). It has previously been reported that both Protein C and antibodies to EPCR (see Stearns-Kurosawa, et al., cited at page 4, line 29) bind specifically to EPCR. Protein C in particular circulates through the body, binding to EPCR as needed. It has been conclusively established that binding occurs at physiological levels of protein C, *in vivo*. *Anyone who has ever cut themself and then not died because the clotting stopped and could subsequently clot when reinjured knows that binding in vivo must occur!* Binding of antibodies *in vivo* has also been demonstrated. Based on the studies in the examples, showing that the conjugates also bind, one skilled in the art would expect the conjugates to bind in the same way when administered *in vivo*. No evidence, only allegations, have been submitted by the Examiner that would lead one skilled in the art to believe otherwise.

It is difficult to see what the difference is in the rejection of claims 5, 6, and 16-18, as compared to the rejection discussed above. **The art cited by the examiner relates to viral vectors; *applicants are not claiming viral vectors nor a method of use thereof.*** In fact, viral

vectors would specifically be excluded from the claims because they would neither bind to EPCR nor selectively bind to EPCR.

The rejections as to antisense and ribozymes is not well founded. Applicants only claim these molecules in a conjugate specifically binding to EPCR; not alone. Moreover, the examiner's rejections indicates a lack of familiarity with the current state of the art, since both antisense and ribozymes are in clinical trial, and efficacy has not only been shown in animals but also people. See the attached abstracts.

Claims 13-25 were rejected on the basis that the only molecules specifically binding EPCR that are enabled are protein C, activated protein C, and antibodies to EPCR. It is certainly clear that these are the major molecules one would use to make these conjugates. Accordingly, solely to faciliate prosecution, claims 13-25 have been limited to conjugates of these molecules.

Claims 1-12 were rejected as not enabled for compounds which bind selectively to EPCR. This rejection ignores the evidence in the examples in the application. Applicants examples have demonstrated the use of activated protein C or antibodies which selectively bind to EPCR. These agents are described in detail at pages 4-5. It is simply non-sensical to conclude otherwise! Protein C only binds to EPCR on the surface of the endothelial cells; antibodies to EPCR are chosen which are selective for EPCR. The term "selective" modifies *binding to the EPCR. No uptake by the nucleus occurs in the absence of binding to the EPCR.*

In contrast to the Examiner's conclusion that the examples do not include controls, controls which show binding *to molecules other than EPCR, specifically thrombomodulin, which are present on the surface of endothelial cells, do not result in uptake to the nucleus.* See page 4, lines 15-24.

Rejections under 35 U.S.C. §112, second paragraph

Claims 1, 5, 12 and 13-25 were rejected under 35 U.S.C. §112, second paragraph, as indefinite. This rejection is respectfully traversed.

Claim 1 has been amended to insert the language of the preamble into the claim body.

Claims 5 and 17 have been amended to delete the 'can be" language.

The term "fragment" is defined by the requirement that the fragment bind to the EPCR. A discussion of fragments is found in the application at pages 5-6. Those skilled in the art of antibodies have been making fragments for about 40-50 years and certainly understand the meaning of the term. Suitable fragments and kits for expression of fragments can be purchased from a variety of suppliers.

Claims 13-25 have been amended as described above to limit their scope. These materials are described in the application and demonstrated in the working examples. Those skilled in the art would have no difficulty in determining what these compounds are.

Rejections under 35 U.S.C. §102(b)

Claims 13-15, 19, 20, 22, 24, and 25 were rejected under 35 U.S.C. §102(b) as disclosed by WO 96/05303. This rejection is respectfully traversed.

WO 96/05303 does not disclose a conjugate having two components:

a molecule selectively binding EPCR and

a molecule to be delivered to the nucleus.

The abstract and Pages 15-16 refer to binding of protein C and activated protein C to EPCR. Page 19 references EPCR labeled with diagnostic labels (note this is EPCR; *not* a molecule binding to EPCR).

Pages 20-21 described antibodies labelled with diagnostic labels. Claims 13-25 (claims 13 and 19) have been amended to exclude antibody conjugates with diagnostic labels.

Pages 23-26 describe molecules binding to EPCR which alter its function. No conjugates are described. Moreover, this is contraindicated by the claim language, since altering the EPCR function would prevent internalization of the conjugate and delivery of the molecules to the nucleus.

Rejections under 35 U.S.C. §102(e)

Claims 13-15, 19-20, and 22-25 were rejected under 35 U.S.C. §102(e) in view of U.S. patent Nos. 5,695,993 and 5,852,171 to Fukudome, et al. This rejection is respectfully traversed.

The abstract and columns 15 and 16 disclose EPCR which may additionally have compounds bound thereto; not compounds binding to EPCR. Therefore the Fukudome, et al., patents do not disclose the claimed conjugate.

Rejections under 35 U.S.C. §103

Claims 16-18 were rejected under 35 U.S.C. §103 as obvious over WO 96/05303, U.S. Patent No. 5,695,993 or U.S. Patent No. 5,852,171 to Fukudome, et al. in combination with Delporte, Antisense & Nucleic Acid Drug Dev. 7, 523-529 (1997) and Rosenkranz, et al., Experimental Cell Res. 199, 323-329 (1992). Claim 21 was rejected as obvious over WO 96/05303, U.S. Patent No. 5,695,993 or U.S. Patent No. 5,852,171 to Fukudome, et al. in combination with Jans, et al., BioEssays 20, 400-411 (1998) and Rosenkranz, et al.These rejections are respectfully traversed.

As discussed before, none of the primary references disclose a conjugate of a compound selectively binding to EPCR with a molecule to be delivered to the nucleus. neither Delporte nor Rosenkranz, et al., make up for these deficiencies.

Rosenkranz describe a conjugate of a protein like insulin and a plasmid, coupled via poly-L-lysine, which is endocytosed when the insulin binds to a cell surface receptor. Nothing in Rosenkranz leads one skilled in the art to select the EPCR as the receptor for uptake of the conjugate into the nucleus, and therefore to select a molecule which selectively binds to the receptor to mediate the uptake.

Delporte discribes triplex forming oligonucleotides which were delivered to epithelial cells using an adenovirus-polylysine complex. Nothing in Delporte would lead one to select large vessel endothelial cells as the target, EPCR as the means for uptake to the nucleus, nor a molecule which selectively binds to EPCR to mediate selective uptake. The cell types are different, the receptor is different, and the targeting compound is not only different but not selective.

In summary, the subject matter of claims 16-18 is not obvious from the cited art.

With respect to claim 21, the art is discussed above except as to Jans, et al. Jans, et al., disclose that certain molecules, such as some growth factors and cytokines, bind to cell surface receptors where they are internalized into the nucleus, to participate in gene regulation. This says nothing about conjugates which are not naturally occuring molecules such as growth factors and cytokines, large vessel endothelium, EPCR and molecules specifically binding thereto, which are not cytokines nor growth factors. Accordingly, there is no teaching that would lead one to substitute EPCR for the receptors of Jans and Hassan, nor molecules which bind to EPCR for the cytokines and growth factors of Jans and Hassan.

In summary, none of the cited art discloses the claimed conjugates or methods of use thereof. Moreover, none makes obvious the claimed conjugates or methods of use since there is

no teaching that would lead one skilled in the art to believe that EPCR would mediate uptake and transport to the nucleus of molecules.

Allowance of claims 1-25, as amended, is earnestly solicited.

Respectfully submitted,

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Certificate of Mailing under 37 C.F.R. § 1.8(a)

I hereby certify that this Amendment, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Date: August 13, 1999

Jean Hicks